REMARKS

Claims 1, 13-17, 19-68, and 70 are currently pending in the application. Claim 17 is canceled. Claims 1, 3, 5, 6, 11, 21, 23, 26, 28, 29, and 70 are amended. Claim 71 is added. The amendments and new claim find support in the specification and are discussed in the relevant sections below. No new matter is added.

Rejection of Claims 1, 3-14, 17, 21-26, 28, 29, and 70 Under 35 U.S.C. §103

The Office Action has rejected claims 1, 3-14, 17, 21-26, 28, 29, and 70 under §103(a) as being obvious over the combination of Grossmann et al. and Kato et al., in view of Hoo et al. Maraskovsky et al., Dullforce et al., Heath et al., McHugh et al., Jacquier-Sarlin et al., and in further view of the teaching in the specification regarding engineering attachment of a lipid to a molecule to permit stable association in the cell plasma membrane.

The rejection is essentially the same as that set forth in the Office Action dated November 3, 2004, with the addition of the reference by Hoo et al. The Office Action asserts that Grossmann et al. teaches transgenic expression of CD40L in neuro-2a tumor cells, wherein the CD40L acts as a costimulator. The Office Action asserts that Kato et al. teaches that CD40-CD40L interaction plays a critical role in immune activation. The Office Action notes, however, that the teachings of Grossman et al. and Kato et al. differ from the claimed invention in that **neither reference teaches a composition comprising an antigen bearing cell and an exogenous engineered ligand for CD40**.

The Office Action asserts that Maraskovsky et al. teaches a method of vaccination with antigen-expressing activated dendritic cells, including stimulating immune responses with the administration of other cytokines such as the CD40 ligand. The Office Action notes that Maraskovsky et al. does not teach the administration of agonistic CD40-specific antibodies. The Office Action asserts that each of Dullforce, Heath, and Caux teaches anti CD40 antibodies which are capable of stimulating immune responses. The Office Action implies that it would have been obvious to one of skill in the art to combine the teachings of anti-CD40 antibodies as taught by Dullforce, Heath, and/or Caux with the "antigen" expressing activated dendritic cells

as taught by Maraskovsky to arrive at the present invention. The Office Action also cites McHugh et al. as teaching methods of introducing the T-cell co-stimulatory molecule B7 into a tumor cell membrane via glycosyl-phosphatidylinositol (GPI). The Office Action asserts that even though McHugh et al focuses on elucidating mechanisms of tumor immunity, one of skill in the art would have been motivated to employ GPI-anchored co-stimulatory molecules with immunogenic cells to vaccinate a mammal. The Office Action also asserts that Hoo et al. teaches "cellular vaccines comprising membrane-bound fusion proteins, including immumodulatory [sic] molecules...fused to a heterologous membrane attachment domain." The Office Action also asserts that Hoo et al. teaches that the vaccine can contain CD40 ligand. Applicants respectfully disagree with the rejection, and submit that there is no teaching or suggestion in any of the cited prior art which would motivate one of ordinary skill in the art to make the proposed combination, and thus, no *prima facie* case of obviousness.

As currently amended, the instant claims relate to a method for vaccinating a mammal against an antigen by administering a composition comprising a cell that bears the antigen and an exogenous engineered ligand for CD40 (the term "exogenous" is defined on page 9, lines 25-26; the term "engineered ligand for CD40" is defined in the specification on page 10, lines 31-2). The engineered ligand for CD40 comprises a ligand for CD40 and a heterologous moiety that binds to the cell when the engineered ligand for CD40 is admixed with the cell. The prior art cited by the Office Action generally falls into two categories: prior art relied on as allegedly teaching a CD40 ligand (Grossmann et al. and Kato et al., in view of Maraskovsky et al., Dullforce et al., and Heath et al.), and prior art relied on as allegedly teaching membrane attachment (McHugh et al. and Hoo). There is insufficient motivation in any of the cited references or in the general knowledge of one of skill in the art to combine the teachings of the cited references in an attempt to arrive at the claimed invention.

Regardless of how combined, Grossmann et al. and Kato et al., in view of Maraskovsky et al., Dullforce et al., and Heath et al. do not teach a method of vaccinating a mammal to an antigen by administering a cell (comprising the antigen) and an engineered ligand for CD40 which includes a heterologous cell membrane binding moiety. None of Grossmann et al. and Kato et al., Maraskovsky et al., Dullforce et al., or Heath et al., regardless of how combined,

teach a membrane associated ligand for CD40. The teachings of each of Grossman et al., Kato et al. and the two Heath et al. references are limited to the endogenous expression of a ligand for CD40, and do not teach a composition comprising an exogenous engineered CD40 ligand and an antigen bearing cell to vaccinate a mammal. Dullforce et al. similarly does not teach or suggest the use of an exogenous engineered ligand for CD40 with an antigen bearing cell to produce a vaccine, and the teachings of Dullforce et al. are limited to the use of an anti-CD40 antibody to act as a specific adjuvant for T cell independent antigens from *Streptococcus pheumoniae, Haemophilus influenzae, and Neisseria meningitides*. Dullforce et al. does not teach or even suggest vaccination using an antigen bearing cell and an engineered ligand for CD40. Moreover, Maraskovsky et al. teaches only **soluble** immunostimulatory molecules and does not teach or even suggest membrane bound immunostimulatory molecules, or that membrane attachment should or could be attempted.

The Office Action asserts that McHugh et al. teaches "the possibility and use [of] recombinant techniques for transmembrane proteins in general and [is] not limited to B7-1." Applicants acknowledge that McHugh et al. states in the Introduction that "[i]t is possible, using recombinant techniques, for transmembrane proteins to be converted to GPI-anchored proteins and incorporated in to cell membranes." The actual teachings provided by McHugh et al., however, are limited to a construct comprising a GPI moiety fused to B7 molecules (also referred to as CD80), and the use of the fusion protein, incorporated into the membrane of tumor cells, to provide a costimulatory signal needed to stimulate T cells. There is simply no teaching in McHugh et al. that would suggest to one of skill in the art to modify the GPI-B7 construct taught therein to generate a GPI-CD40 ligand construct, particularly since the CD40 ligand prior art cited by the Office Action specifically teaches either endogenous CD40 ligand or soluble CD40 ligand. McHugh does not teach, suggest, or even mention a ligand for CD40. Moreover, there is no teaching or suggestion in McHugh et al. of using the GPI-B7 fusion to vaccinate a mammal against an antigen; McHugh et al. merely use the GPI-B7 fusion to supplement deficient B7 production in tumor cells. It is also important to note that the mode of operation of B7 is separate and distinct from a ligand for CD40. B7 functions as a molecule on an antigen presenting cell (following engulfment of tumor cells and antigen presentation) that binds to T-cells. In contrast, CD40 ligand is expressed on T-cells and binds to APCs; that is, the two

systems work in opposite directions (See, e.g., Schoenberger et al. 1998 Nature 393:480-3). Moreover, the Office Action asserts that McHugh et al. would motivate one of skill in the art to utilize other co-stimulatory molecules in place of B7. In fact, CD40 ligand is not a co-stimulatory molecule; CD40 is the costimulatory molecule (Schoenberger et al.) which binds to CD40 ligand present on T-cells. Thus, the disclosure in McHugh et al. of the use of the costimulatory molecule B7 would not motivate one of skill in the art to substitute B7 with a non-costimulatory molecule such as CD40 ligand. In addition, there is no general teaching in McHugh et al. of the use of GPI-linked molecules to vaccinate a mammal. The fact that McHugh et al. teaches that it is technically feasible to produce a GPI-B7 fusion protein is not sufficient motivation to suggest to one of skill in the art to make an exogenous engineered CD40 ligand for use in vaccinating a mammal as required by the instant claims.

The Office Action now cites Hoo to supplement the rejection for alleged obviousness. The Office Action asserts that Hoo has been added to address Applicant's arguments with respect to the recitation of "a ligand for CD40 which comprises a heterologous cell membrane binding moiety." The Office Action asserts that Hoo teaches "cellular vaccines comprising membrane-bound fusion proteins, including immunomodulatory molecules...fused to a heterologous membrane attachment domain." The Office Action also asserts that Hoo teaches that the vaccine can contain CD40 ligand. There is insufficient motivation to combine the teachings of Hoo with the prior art of record in an attempt to arrive at the claimed invention.

The teaching of Hoo are restricted to endogenous expression of a fusion protein having a transmembrane domain and a non-antibody immunomodulatory molecule. With respect to the currently elected species of anti-CD40 antibody. Hoo specifically teaches away from the claimed invention because Hoo teaches fusion proteins comprising **non-antibody** immunomodulatory molecules fused to transmembrane domains. With respect to the broader genus of ligands for CD40, Hoo does not teach or even suggest an engineered ligand for CD40 fused to a heterologous moiety that binds to a cell. Although Hoo mentions CD40 ligand at column 18, line 65, a reading of the preceding and following paragraphs makes clear that Hoo is teaching that the vaccine composition, in addition to the non-antibody immunomodulatory fusion protein, can also include CD40 ligand. Hoo does not teach that CD40 ligand is incorporated into

the fusion protein, but that it is provided **in addition** to the fusion protein. Because Hoo does not teach or even suggest an engineered ligand for CD40 as currently claimed, and does not teach or even suggest a method of vaccinating a mammal by administering an engineered ligand for CD40 and an antigen bearing cell, Hoo does not provide the requisite disclosure to motivate one of skill in the art to combine the prior art in the manner suggested by the Office Action.

The Office Action asserts that the required motivation to combine the teachings of the cited references is provided by the specification's disclosure that it was well known to engineer the attachment of a lipid to a molecule such as a peptide to permit the complex to be stably associated with a cell membrane. Applicant respectfully disagrees. It is well established law that the level of skill in the art (e.g., the technique for modifying a CD40 ligand to include a cell membrane binding moiety) cannot be relied upon to provide the suggestion to combine references (*Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999)). Thus, the mere fact that the technology existed to modify a protein to be incorporated into a cell membrane does not provide the level of motivation necessary to make the combination suggested by the Office Action.

The Office Action has also cited Jacquier-Sarlin et al., which teaches the use of complement fragments including C3b to enhance immune responses to antigens of interest, as rendering obvious claims 3 and 4, drawn to including with the CD40 ligand-enhanced cell of claim 1, an opsonin-enhanced cell. Applicant respectfully disagrees. Jacquier-Sarlin et al merely teaches the ability of the complement fragment C3b to modulate antigen processing, and then **only when fused to the antigen**. There is no requirement in the instant claims for fusion of an opsonin to an antigen of interest, only that the vaccine composition include an opsonin-enhanced cell (defined at page 3 of the specification as "cells which have been 1) modified so as to express an opsonin from a recombinant nucleic acid, 2) modified so as to express higher levels of an endogenous opsonin, or 3) mixed with an exogenous opsonin"). Jacquier-Sarlin et al. does not teach an opsonin-enhanced cell, and moreover does not teach or even suggest a engineered CD40 ligand of the present invention.

Whether considered alone or in combination, none of the prior art cited by the Office Action provides sufficient disclosure to motivate one of skill in the art to combine the individual, unrelated teachings of each reference in an attempt to arrive at the claimed invention. Accordingly, the instant claims are not obvious in view of the cited prior art, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

Date: 12/23/05

Name: Matthew Beaudet
Registration No.: 50,649
Customer No.: 29933
Edwards Angell Palmer & Dodge LLP
111 Huntington Avenue
Boston, MA 02199-7613
Tel. (617) 239-0100